

Remarks

The Office Action modified the restriction requirement of Paper No. 5 “such that the elected restricted group will include only claims 12-16 which read on the elected species “and claims 1-6, 8 and 15-31 were withdrawn from consideration.

This is not understood since the elected species was the compound of claim 26 ((3S)-3-[(1-(2-chlorobenzyl)-4-hydroxy-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)amino]carbonyl)amino]-3-(4-methylphenyl)propanoic acid). In view of this election, how can claim 26 be withdrawn? Pursuant to this election, applicants identified all the claims readable thereon (claims 1-19, 25, 26, 30 and 31). It appears that the Examiner has arbitrarily withdrawn claims, including the elected species claim. This is believed to be improper. Reconsideration is requested.

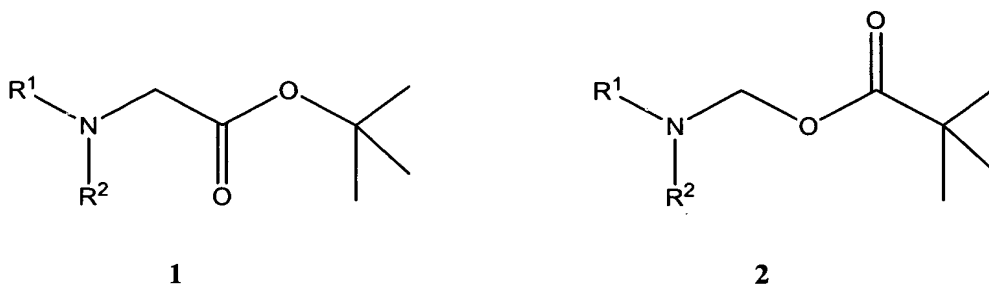
The Office Action has rejected claims 12-16 under 35 U.S.C. §112, first paragraph, as not being enabled for certain embodiments. Applicants have amended the claims to specify the election donating and election withdrawing which are clearly supported by the disclosure. Additionally, claims 3, 6, 9, 13, 16 and 18 have been canceled and other substituents have been amended to specify those which are clearly supported. Thus, claims 1, 2, 4, 5, 7, 8, 10-12, 14, 15, 17, 19, 25, 26, 30 and 31, as presented amended, are enabled and the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

The rejection of claims 13 and 16 under 35 U.S.C. §112, second paragraph, is moot in view of the cancellation of these claims.

The Office Action rejected claims 12-16 under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 5,521,179 to Bernstein et al. in view of Greene. The Office Action stated that the “difference between the prior art compound and the instantly claims compounds” is the protecting group on the pyridine portion.

Bernstein et al. discloses the possibility of an -NHCONHCOOH substituent in the 3-position of the pyridone ring. Our substituent, -NHCONH-CH(TLR⁴)CR⁹R¹⁰COOH, in that position is more substantial than the Bernstein et al substituent. Additionally, the carbamic acid disclosed in Bernstein et al. would be unstable, quickly losing carbon dioxide, leaving only -NHCONH₂ as the remaining substituent. This is even further removed from our compounds of interest. This is not an obvious structural change. Apparently, the Office Action has incorrectly interpreted the structure for the N-pivaloyloxymethylamine protecting group on p. 271 of Greene. It appears that the structure has been interpreted to be 1 below whereas it is actually the acetal 2. Since compounds with substituents like 2 are not disclosed

by Bernstein et al., then these references are not properly combinative when considering our application.



Predictability of the state of the art:

The Office Action states that the state of prior art regarding therapy for diseases mediated by $\alpha_4\beta_1$ remains unpredictable, citing the fact that natalizumab failed to meet the primary endpoint in a Phase II clinical trial for Crohn's disease. Recently, Biogen announced that new data shows that natalizumab did have a drug effect in Crohn's disease and that the failure to meet the primary endpoint in the ENACT-1 trial was due to a high placebo rate (*BioWorld Today*, May 20, 2004, p 1, 3). Based on this and the positive results of natalizumab in trials for multiple sclerosis, it appears that there is predictability in the state of the art. The Office Action also states that chronic inhibition of $\alpha_4\beta_1$ could cause embryonic mortality prior to birth, suggesting that the use of $\alpha_4\beta_1$ inhibitors should be avoided during pregnancy. Recent papers suggest that some classes of small molecule $\alpha_4\beta_1$ antagonists do not cause this teratogenic effect [Spence, S. et al. *Teratology* **65**, 26-37; Crofts, F. et al. *Birth Defects Res. B* **71**, 55-68; Crofts, F. et al. *Birth Defects Res. B* **71**, 69-79]. In these papers, procedures are described to help determine a compound's teratogenic effects when delivered to pregnant animals.

The examiner states that it is unclear whether promoting or inhibiting $\alpha_4\beta_1$ would be beneficial in treating diseases. Inhibiting antibodies of α_4 integrins has been shown to be effective treatments in animal models of asthma [rat: Hojo, M. et al. *Am. J. Respir. Crit Care Med.* **158**, 1127-1133 (1998); mouse: Henderson, W.R. et al. *J. Clin. Invest.* **100**, 3083-3092 (1997); guinea pig: Pretolani, M. et al. *J. Exp. Med.* **180**, 795-805 (1994); rabbit: Metzger, W.J. *Springer Semin. Immunopathol.* **16**, 467-478 (1995); sheep: Abraham, W.M. et al. *J. Clin. Invest.* **93**, 776-787 (1994)], multiple sclerosis [Engelhardt, B. et al. *J. Clin. Invest.* **102**, 2096-2105 (1998); Yednock, T.A. et al. *Nature* **356**, 63-66 (1992); Kent, S.J., Karlik, S.J., Rice, G.P. & Horner, H.C. *J. Magn Reson. Imaging* **5**, 535-540 (1995); Kent, S.J.

et al. J. Neuroimmunol. 58, 1-10 (1995)], Crohn's disease [Podolsky, D.K. *et al. J. Clin. Invest. 92, 372-380 (1993)*], diabetes [Baron, J.L. *et al. J. Clin. Invest. 93, 1700*; Burkly, L.C. *et al. Diabetes 43, 529*], contact hypersensitivity [Chisholm, P.L. *et al. Eur. J. Immunol. 23, 682*] and cardiac allograft rejection [Isobe, M. *et al., J. Immunol. 153, 5810*]. Peptide inhibitors of $\alpha_4\beta_1$ have been shown efficacious in animal models of contact hypersensitivity [Ferguson, T.A. *et al. Proc. Natl. Acad. Sci. USA 88, 8072*], arthritis [Wahl, S.M. *et al. J. Clin. Invest. 94, 655*] and cardiac allograft rejection [Molossi, S. *J. Clin. Invest. 95, 2601*]. Based on these reports, one skilled in the art would predict that the inhibition of $\alpha_4\beta_1$ by a small molecule would be beneficial in treating these diseases. Copies of these articles will be provided upon request.

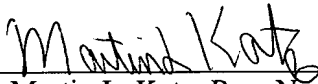
As the small molecules disclosed in the instant application show inhibitory activity against $\alpha_4\beta_1$ in *in vitro* experiments as detailed in Tables 2-7, one would predict that they would be beneficial in treating the previously mentioned diseases.

In view of the above comments, withdrawal of the Section 103(a) rejection is deemed appropriate.

Favorable consideration and allowance of claims 1, 2, 4, 5, 7, 8, 10-12, 14, 15, 17, 19, 25, 26, 30 and 31 is respectfully requested.

If any additional fees are incurred as a result of the filing of this paper, authorization is given to charge deposit account number 23-0785.

Respectfully submitted,


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I hereby certify that the Amendment is being deposited with the U.S. Postal Service via First Class Mail to: Commissioner for Patents, Washington, D.C. 20231 on September 17, 2004.


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